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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 45

Application Number: 08405454
Filing Date: 3/15/95
Appellant(s): Sullivan et al.

Michael Siekman
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 5/6/99.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct. However, said statement erroneously refers to application "07/124438" on page 4 of the Brief, wherein the application referred to is actually 06/659629. Said statement also refers to an amendment filed "August 5, 1997", wherein said amendment was actually filed August 5, 1998.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims cited in each of the three pending rejections stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Sullivan et al., Proc. West. Pharmacol. Soc., vol. 25, (1982), pp. 185-192.

Smith et al., Clin. Exp. Immunol., vol. 36, (1979), pp. 384-396.

Coulter et al., J. Immunol. Methods, vol. 59, (1983), pp. 199-203.

Stedman's Medical Dictionary, 23rd Edition, Williams and Wilkins Co., (1976), pp. 94.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 40-42, 45-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "essentially free from contaminating Fc" in claims 40 and 45. The specification and original claims 27 and 29 do not recite that the claimed F(ab) are essentially free from contaminating Fc. They recite that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

Rejections Under 35 U.S.C. § 103

A) Claims 40-42,45-47 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977).

Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) containing antivenin. The amendment filed 5/4/98, pages 3 and 4 establishes that the art recognized that the terms "antivenin" and "antivenom" refer to the same product.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). Stedman's Medical Dictionary defines antivenin as "an antitoxin specific for an animal or insect toxin"(page 94). Therefore the composition taught by Coulter et al. is an antivenin. The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure.

Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications (see page 393, first paragraph, *Discussion* section). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced antivenom compositions consisting of F(ab) fragments because Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus, Coulter et al. teaches a method for producing antivenin F(ab) fragments that are free of Fc, and Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications. One of ordinary skill in the art would have been motivated to do the aforementioned because Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG. For urgent clinical situations such as life threatening digitalis-toxic cardiac arrhythmias, the present study indicates that Fab has another important advantage-more rapid and extensive distribution to its presumed site of action in the interstitial space." (page 393). Further motivation is provided by the teaching of Coulter et al. that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). In addition, Sullivan et al. teach that

reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph).

B) Claims 45-47 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

The claims are drawn to F(ab) fragments. Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) against Crotalus venom.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure. Coulter et al. teach that: "Fab fragments of

IgG have been used in enzyme immunoassay instead of IgG (Kato et al. 1976). EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." (page 199, first paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed F(ab) fragments because Coulter et al. teaches that: "EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme" and therefore a routineer would have produced the F(ab) against Crotalus venom for use in EIAs to detect said venom.

(11) Response to Argument

Rejections Under 35 U.S.C. § 112, First Paragraph

Regarding appellants comments, there is no disclosure in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification and original claim 27 discloses that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen. There is no disclosure in the specification as originally filed of the scope of the claimed invention wherein the claimed invention is essentially free from contaminating Fc. Regarding appellants comments about the four-hour

digest in Figure 4 of the specification, said preparation is not "essentially free from contaminating Fc as determined by immunoelectrophoresis" because it contains detectable levels of Fc as determined by immunoelectrophoresis. The particular passage of the specification to which appellant refers discloses that a "slight hind of an F(c) reaction was detected in the 4 hour digest". Furthermore, the particular experiment which applicant refers to discloses a particular preparation generated under a particular set of conditions wherein said preparation shows a "slight hind of an F(c) reaction was detected in the 4 hour digest". Regarding appellants comments about what the term "essentially free from contaminating Fc" means, appellant has argued that the term is as defined in the MPEP section 2111.03. However, said section of the MPEP refers to the term "consisting essentially of" and the legal definition of said term. The term "consisting essentially of" is not recited in the claims under consideration. Furthermore, the terms "consisting essentially of" and "essentially free" are not synonymous. The MPEP section 2111.01 (Rev. 1, Feb. 2000) discloses that:

In re Marosi, 710 F.2d 799,218 USPQ 289 (Fed. Cir. 1983) ("Claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their broadest reasonable interpretation." 710 F.2d at 802, 218 USPQ at 292 (quoting In re Okuzawa, 537 F.2d 545, 548, 190 USPQ 464, 466 (CCPA 1976))(emphasis in original). The court looked to the specification to construe "essentially free of alkali metal" as including unavoidable levels of impurities but no more.).

The term "essentially free from contaminating Fc" is not defined in the specification. Based on the definition of said term arrived as per *In re Marosi*, Example 4 in the specification does not disclose a F(ab) preparation that is "essentially free from contaminating Fc", because it contains detectable levels of Fc as determined by immunoelectrophoresis. Furthermore, there is no disclosure in the specification that the claimed invention would be limited to Fc present in *"unavoidable levels of impurities but no more"*.

Rejections Under 35 U.S.C. § 103

A) Claims 40-42,45-47 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977).

Regarding appellants comments in pages 17-19 of the instant Brief, Sullivan et al. teach purified antivenom polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). Sullivan et al. disclose that said preparation can be used as antivenom to treat Crotalidae envenomation (see page 185, first paragraph). Thus, while Crotalidae venom contains a complex mixture of toxins, the antivenom taught by Sullivan et al. contains all the necessary antibodies to neutralize the toxicity of said mixture. Coulter et al. teach that F(ab) which neutralizes a large molecular

weight protein snake toxin can be made and that said antivenom can work in vivo to neutralize snake toxin (see page 202, third paragraph). Smith et al. teach that Fab fragments can be used to neutralize digoxin (low molecular weight potential toxin)(see *Summary*). Smith et al. also teaches that relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance (see page 393, *Discussion* section) indicating that Smith et al. believed that Fab could be used for the neutralization of toxic substances other than digoxin. Furthermore, Smith et al. indicated that Fab and the intact antibody from which the Fab were derived would be expected to have similar binding properties (see page 393, *Discussion* section). Thus, the art recognized that when an intact antibody has been shown to have the capability of neutralizing a toxin, that the Fab derived from said antibody will also be able to neutralize said toxin. Furthermore, based on the teachings of Coulter et al. and Smith et al. it appears that use of Fab to neutralize toxin (wherein the intact antibody had already been shown to be capable of neutralizing said toxin) would be equally applicable to large and small toxin molecules. There is no actual evidence of record that establishes that it would be unpredictable whether Fab derived from a known antivenom would have antivenom activity seen in the preparation from which it was derived.

Regarding appellants comments in pages 20-23 of the instant Brief, the following comments are made. Regarding $F(ab)_2$ containing antivenom, the claimed invention is not drawn to $F(ab)_2$ it is drawn to Fab. However, regarding the Smith declaration and $F(ab)_2$ based antivenom, there is no teaching in said declaration that $F(ab)_2$ based antivenom are less

effective than whole immunoglobulin based antivenom. In fact, the Smith declaration indicates that such preparations have been sold (and presumably used) since 1969 (see section 7). Regarding comments about $F(ab)_2$ in the First Russell declaration and Sullivan declarations, said **statements are directly contradicted by their own statements in the instant application** (Sullivan and Russell are the inventors of the instant application). For example, the specification, page 8, lines 5-8 state:

"Such $F(ab)_2$ fragments should also afford greater protection against venom-induced pathophysiology than the commercial antivenin."

Also see original claim 28 which is drawn to a $F(ab)_2$ antivenin against Crotalus. Thus appellants arguments regarding the issue of $F(ab)_2$ antivenom versus intact antibody antivenom are contradicted by the teachings of their own specification.

Regarding appellants comments about "venom depot effect", Smith et al. disclose that because of smaller size, administered Fab are actually more rapidly and extensively distributed throughout the body than IgG (see page 395). Thus, Fab would actually be more likely to reach toxins distributed in various nonvascular compartments of the body. Regarding the kinetics of elimination of Ig versus Fab, Smith et al. teach that rapid clearance of Fab "can be used to advantage when the object is rapid neutralization and clearance of a toxic substance" (see page 393). Regarding the issue of bivalency of $F(ab)_2$, there is no evidence of record that cross linking of antibody fragments is required for toxin neutralization. Certainly, both Smith

et al. and Coulter et al. which demonstrate toxin neutralization using Fab, would contradict the need for cross linking of antibody binding fragments for toxin neutralization.

Regarding appellants comments in pages 23-27, said comments are based on an erroneous interpretation of the Faulstich et al. and Balthazar et al. publications. Regarding the Faulstich et al. reference said reference teaches that **monoclonal antibody against alpha amatoxin cannot be used to treat alpha amatoxin** and that **F(ab) obtained from said antibody also cannot be used to treat alpha amatoxin**. Thus, the circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because Sullivan et al. teach that the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Regarding comments about Balthasar et al., Balthasar et al. refer to alpha amatoxin, **which is a toxin which cannot be treated with antibodies as shown by Faulstich et al.** The circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Furthermore, Balthasar et al. teach that the use of drug-binding antibodies and antibody fragments for the treatment of drug intoxication is well known. (see Abstract, last sentence). In addition, Coulter et al. teach that F(ab) which neutralizes a large molecular weight protein snake toxin can be made and that said antivenom can work in vivo to neutralize snake toxin

(see page 202, third paragraph). The various comments in the First Russell declaration and Sullivan declaration about why Fab would not work as disclosed in pages 23 and 24 of the instant Brief are based on the aforementioned misinterpretation of the data provided in the Balthasar et al. and Faulstcih et al. references. In the absence of support from the Balthasar et al. and Faulstcih et al. references, the hypotheses about why Fab would not work are unsubstantiated allegations. There is no evidence of record that Fab derived from an Ig antivenom which neutralized toxin would have any negative effect when said Fab were administered in vivo. Regarding appellants comments that the experiments disclosed by Coulter et al. used toxin and antibody or Fab that were first mixed before in vivo injection, the art already recognized that the antivenom from which the Fab would have been derived could bind Crotalus venom, and Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. Furthermore, if a deleterious systemic redistribution of Fab/venom complexes in vivo was to occur, it would have occurred in the experiments disclosed by Coulter et al., because the complexes were present in vivo. Regarding comments about Sorkine et al., Sorkine et al. disclose that Fab was successfully used to neutralize toxin in vivo, irregardless of whether the assay used premixing of Fab and toxin or separate in vivo administration of Fab and toxin. Sorkine et al. disclose that "One explanation is the different kinetics of these fragments. The smaller size of Fab results in faster diffusion and a greater volume of distribution".

Thus, Sorkine et al. confirm the teachings of Smith et al. that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. In addition, the art already recognized that the antivenom from which the Fab would have been derived could bind Crotalus venom, and Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. Furthermore, Sorkine et al. actually confirm that with regards to Fab that the in vitro mixture of the antibody and toxin prior to administration mirrors the effect seen when Fab and toxin are administered separately in vivo. Regarding appellants comments, antisera against Crotalus toxin which contained antibodies to neutralize said toxin/toxins was already known in the art. Smith et al. teach that F(ab) are less immunogenic than the antibody from which they are derived (see page 395). Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG." (page 393).

Thus, appellants arguments are based on misinterpretations of the Faulstich et al. and Balthazar et al. references and declarations from Russell and Sullivan which provide various unsupported hypotheses about why Fab antivenom would not work, without providing any evidence to support said conjecture. In addition, the Russell and Sullivan declarations actually

contradict some of the very statements made in the specification (eg. see comments regarding $F(ab)_2$).

B) Claims 45-47 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

Regarding appellants arguments as they apply to the instant rejection, the claimed invention under consideration is not drawn to an antivenom. It is drawn to a Fab antibody. Whether or not an antivenom based on the Fab recited in the claims could be used to treat snake bites in vivo is not germane to the claimed invention because the claimed Fab can be used in in vitro assays. Coulter et al. teach that: "Fab fragments of IgG have been used in enzyme immunoassay instead of IgG (Kato et al. 1976). EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." (page 199, first paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed F(ab) fragments because Coulter et al. teaches that: "EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme" and therefore a routineer would have produced the F(ab) against Crotalus venom for use in EIAs to detect said venom.

There has been no evidence of record submitted which indicates that the claimed Fab could not be used in immunoassays. Coulter et al. teaches that: "EIAs of higher sensitivity

have been claimed when Fab enzyme is used instead of IgG enzyme" and therefore a routineer would have produced the F(ab) against Crotalus venom for use in EIAs to detect said venom.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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